Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Nevirapine (Viramune, NVP)

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Animal Studies

Carcinogenicity

NVP showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. The occurrence of hepatocellular adenomas and carcinomas increased at all doses of NVP in male mice and rats and at higher doses of NVP in female mice and rats. Systemic exposure to NVP at all studied doses was lower in rodents than the systemic exposure observed in humans who received therapeutic doses. Given the lack of genotoxic activity of NVP, it is unclear whether the appearance of hepatocellular neoplasms in NVP-treated mice and rats is relevant to humans.[1]

Reproduction/Fertility

Female rats showed evidence of impaired fertility at systemic exposures to NVP that were comparable to therapeutic exposures in humans.[1]

Teratogenicity/Adverse Pregnancy Outcomes

In reproductive studies of rats and rabbits, no teratogenic effects of NVP have been observed at systemic exposures approximately equivalent to or 50% greater than the systemic exposure (based on area under the curve [AUC]) seen in humans who received the recommended dose. In pregnant rats, however, a significant decrease in fetal weight occurred at doses that produced systemic concentrations approximately 50% higher than human therapeutic exposure.[1]

Human Studies in Pregnancy

Pharmacokinetics

The pharmacokinetics (PKs) of NVP have been evaluated in pregnant women who received NVP as part of antiretroviral therapy (ART) during pregnancy. A study that evaluated NVP PKs in 26 women during pregnancy (which included seven women in their second trimester and 19 women in their third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter NVP PK parameters.[2] In contrast, NVP clearance was 20% greater, AUC was 28% lower, and maximum plasma concentration was 30% lower in 16 pregnant women than in 13 nonpregnant women during a therapeutic drug monitoring program that collected plasma samples over a 12-hour period. The authors of that study also reported high variability in plasma NVP concentrations.[3] A Dutch study reported a nonsignificant trend toward lower NVP exposure during pregnancy, with a median steady-state NVP concentration of 5.2 mcg/mL in 45 pregnant women compared to a median of 5.8 mcg/mL in 152 nonpregnant women ($P = 0.08$).[4] An intensive PK study of 59 women found that pregnant women who had one or two mutations in cytochrome P (CYP) 2B6 had higher NVP clearance than a different group of postpartum women who had one or two mutations in CYP2B6.[5] In fast metabolizers who had no mutations in CYP2B6, no differences in NVP exposure were seen between pregnant women and postpartum women. No dose adjustment is currently recommended for NVP during pregnancy.

Placental and Breast Milk Passage

NVP demonstrates rapid and effective placental transfer, achieving near-equivalent concentrations in maternal and cord blood (cord blood-to-maternal-plasma ratio ranges from 0.60–1.02).[6,7]

NVP has also been shown to be excreted into human breast milk. In a study of 57 Malawian women who received postpartum NVP-based therapy, the breast milk-to-maternal-plasma concentration ratio was approximately 0.6; detectable NVP concentrations were found in the breastfeeding infants (interquartile range 0.54–1.06 mcg/mL).[8] In data from 15 breastfeeding women who received NVP-based therapy in Botswana, median maternal plasma concentration of NVP at 1 month postpartum was 6.71 mcg/mL and median maternal breast milk concentration was 1.83 mcg/mL, for a median maternal breast milk-to-plasma

ratio of 0.27.[9] Infant exposure was measured at 1 month in nine infants; all infants had biologically significant, detectable NVP concentrations in their blood, with a median level of 0.37 mcg/mL (and a range of 0.24–1.2 mcg/mL), representing approximately 6% of the median maternal value. Similar data were reported in a study of 67 mothers who received NVP-based therapy in Kenya; the median concentration of NVP in breast milk was 4.55 mcg/mL, with median concentrations in breastfeeding infants of 0.99 mcg/mL at 2 weeks postpartum, 1.03 mcg/mL at 6 weeks postpartum, and 0.73 mcg/mL at 14 weeks postpartum.[10] An additional study in 122 Nigerian mother-infant pairs found that the median breast milk-to-plasma NVP AUC ratio was 0.95 (with a range of 0.56–1.5).

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to NVP in humans have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a two-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. No such increase in the risk of birth defects has been observed in infants who were exposed to NVP. Among the cases of first-trimester NVP exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.80% (32 of 1,153 births; 95% confidence interval [CI], 1.9% to 3.9%) compared with a total prevalence of 2.72% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[11] Similarly, the French Perinatal Cohort reported no association between exposure to NVP and birth defects with 71% power to detect a 1.5-fold increase.[12]

Other Safety Information

Severe, life-threatening, and (in some cases) fatal hepatotoxicity—including fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure, and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome—have been reported in patients with HIV who were receiving NVP in combination with other drugs for treatment of HIV and in a small number of individuals who were receiving NVP as a component of postexposure prophylaxis of nosocomial or sexual exposure to HIV.[13] In general, clinical hepatic events, regardless of severity, have occurred in 4.0% of patients (with a range of 0% to 11.0%) who received NVP in controlled clinical trials; however, the risk of NVP-associated liver failure or hepatic mortality has been lower, ranging from 0.04% to 0.40%.[1,14] The greatest risk of severe rash or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past this period and patients should be regularly monitored for signs of toxicity.

Incidence of severe NVP-associated skin rash has been reported to be 5.5 times to 7.3 times more common in women than men, and cases have been reported in pregnant women.[15-17] Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2 times more common in women than men.[14] Several studies suggest that the degree of risk of hepatic toxicity varies with CD4 T lymphocyte (CD4) cell count. In a summary analysis of data from 17 clinical trials of NVP therapy, women with CD4 counts >250 cells/mm^3 were 9.8 times more likely to experience symptomatic, often rash-associated, NVP-related hepatotoxicity than women with lower CD4 counts.[14] Higher CD4 counts have also been associated with an increased risk of severe, NVP-associated skin rash.[16]

Rates of hepatotoxicity and rash similar to those in U.S. studies have been seen in international cohorts of nonpregnant women, although not all studies have reported an association between rates of hepatotoxicity and rash and CD4 counts >250 cells/mm^3.[18] In a study of 359 nonpregnant women who were randomized to receive NVP-based therapy in sub-Saharan Africa, higher NVP exposure was associated with the development of severe skin toxicity, and baseline CD4 counts ≥250 cells/mm^3 were associated with the development of NVP-related liver toxicity and drug discontinuation.[19] Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants), TRAF proteins, and immune human leukocyte antigen loci may be associated with a higher risk of NVP-associated adverse events, and that the relationship between genetic variants and adverse events may vary by race.[20-23] Published literature indicates that rash and hyperbilirubinemia have been seen in infants who were exposed to NVP through breastmilk.[1]

Although fatal cases of hepatic failure have been reported in pregnant women with HIV who were receiving

NVP as part of an ART regimen, it is uncertain whether pregnancy increases the risk of hepatotoxicity in women receiving NVP or other antiretroviral drugs.[24] In a systematic review of 20 studies that included 3,582 pregnant women from 14 countries who initiated NVP while pregnant, the pooled proportion of women who experienced a severe hepatotoxic event was 3.6% (95% CI, 2.4% to 4.8%) and the proportion of women who experienced severe rash was 3.3% (95% CI, 2.1% to 4.5%); overall, 6.2% of women stopped taking NVP due to an adverse event (95% CI, 4.0% to 8.4%).[25] These results were comparable to published frequencies in the general adult population and comparable to frequencies in nonpregnant women within the same cohorts. These data suggest that women who take NVP during pregnancy do not experience adverse events more frequently than the general population of people who take NVP. This is consistent with data from two multicenter prospective cohorts in which pregnancy was not associated with an increased risk of NVP-associated hepatic toxicity.[26,27] In contrast, an analysis of data collected in the United Kingdom and Ireland from 2000 to 2011 evaluated 3,426 women, one-quarter of whom were pregnant, and found that pregnant women who were taking efavirenz, maraviroc, or NVP had an increased risk of liver enzyme elevation.[28]

The systematic review discussed above also reported an increased likelihood of cutaneous events (odds ratio [OR] 1.1; 95% CI, 0.8–1.6) and severe cutaneous adverse events in pregnant women with CD4 counts ≥250 cell/mm^3 (OR 1.4, 95% CI, 0.8–2.4); however, these trends were not significant.[25] A separate systematic review of 14 studies did report a significant association between increased toxicity risk and the initiation of NVP-based therapy during pregnancy in women with CD4 counts ≥250 cells/mm^3.[29] A small case-control study (six cases, 30 controls) in South Africa reported that pregnancy increased the chance of developing Stevens-Johnson syndrome (OR 14.28, $P = 0.006$; 95% CI, 1.54–131.82).[30] NVP (as a component of a combination regimen) should be initiated in pregnant women with CD4 counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. Women with CD4 counts <250 cells/mm^3 can receive NVP-based regimens, and women who become pregnant while taking NVP and who are tolerating their regimens well can continue using those regimens, regardless of their CD4 counts.

In a chart abstraction study that used data collected at eight government hospitals in Botswana, women who received ART regimens that contained NVP were more likely to experience certain adverse events than women on ART regimens that did not contain NVP, including hypertension (30% vs. 16%), severe hypertension (3.3% vs. 1.2%), gestational hypertension (18% vs. 10%), and early gestational hypertension (12% vs. 7%).[31]

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity (i.e., pregnancy-related nausea and vomiting), health care providers who are caring for pregnant women who are receiving NVP should be aware of this potential complication. Frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) is necessary, particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, and then monthly for the first 18 weeks; in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter.[32] Transaminase levels should be checked in all women who develop a rash while receiving NVP. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe transaminase elevations should stop taking NVP and not receive the drug in the future.

Additional Information

In a nonrandomized parallel-group study of etonogestrel exposure in women who were on ART, NVP had no effect on etonogestrel levels; in contrast, lower levels of etonogestrel were seen in recipients who were taking efavirenz.[33]

Excerpt from Table 8

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Nevirapine (NVP) *Viramune* *Viramune XR* **Note:** Generic products are available for some formulations.	**NVP (Viramune)** *Tablet:* • 200 mg[d] *Oral Suspension:* • 50 mg/5 mL[d] **Viramune XR** *Tablets:* • 100 mg • 400 mg[d]	**Standard Adult Doses:** • NVP 200 mg once daily (using Viramune immediate release) for a 14-day lead-in period; thereafter, NVP 200 mg twice daily or 400 mg (using Viramune XR tablet) once daily, without regard to food. • Repeat lead-in period if therapy is discontinued for >7 days. • In patients who develop mild-to-moderate rash without constitutional symptoms during the lead-in period, continue lead-in dosing until rash resolves, but administer for ≤28 days total. **Pregnancy** *PKs in Pregnancy:* • PKs of immediate-release tablets not significantly altered in pregnancy. • No data available on extended-release formulations in pregnancy. *Dosing in Pregnancy:* • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and two-fold increase in cardiovascular and genitourinary defects). There is an increased risk of symptomatic liver toxicity when first initiating therapy in women with CD4 counts ≥250/mm^3. Liver toxicity is often associated with a rash and can be fatal. Pregnancy does not appear to increase this risk. NVP should be initiated in pregnant women with CD4 counts ≥250 cells/mm^3 only if benefit clearly outweighs risk. There is a potential increased risk of life-threatening hepatotoxicity in women with high CD4 counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity. Women who become pregnant while taking NVP-containing regimens and who are tolerating their regimens well can continue taking those regimens, regardless of their CD4 counts.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

[d] Generic formulation available.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic XR = extended release

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